Pre-Clinical Murine Models of Colitis

Subjects: Immunology

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Crohn's disease (CD) and ulcerative colitis (UC) are both highly inflammatory diseases of the gastrointestinal tract, collectively known as inflammatory bowel disease (IBD). Although the cause of IBD is still unclear, several experimental IBD murine models have enabled researchers to make great inroads into understanding human IBD pathology. Murine experimental models of human IBD exhibit immune pathological signatures resembling Crohn's disease (CD) or ulcerative colitis (UC). These models include the chemical-induced trinitrobenzene sulfonic acid (TNBS) model, oxazolone and dextran sulfate sodium (DSS) models, the gene-deficient I-kappa-B kinase gamma (Ikk-γ) and interleukin(IL)-10 models, and the CD4+ T-cell transfer model. Although most pre-clinical murine models do not fully recapitulate the complexity of human IBD, these models have added to our knowledge about the causes of disease and have provided targets for developing new treatments.

inflammatory bowel disease ulcerative colitis Crohn's disease murine models

1. Introduction

The use of pre-clinical murine models of human IBD is currently employed by researchers to better understand disease etiology. Murine experimental models of human IBD exhibit immune pathological signatures resembling Crohn's disease (CD) or ulcerative colitis (UC). These models include the chemical-induced trinitrobenzene sulfonic acid (TNBS) model, oxazolone and dextran sulfate sodium (DSS) models, the gene-deficient I-kappa-B kinase gamma (Ikk-γ) and interleukin(IL)-10 models, and the $CD4^+$ T-cell transfer model [1][2][3][4][5][6]. Although most pre-clinical murine models do not fully recapitulate the complexity of human IBD, these models have added to the knowledge about the causes of disease and have provided targets for developing new treatments.

2. Chemical Induced Colitis

2.1. Oxazolone Colitis

Oxazolone colitis (OC) is induced by the intrarectal administration of a haptenising agent known as oxazolone (4-ethoxymethylene-2-phenyl-2-oxazolin-5-one) in ethanol (**Figure 1**) [1].

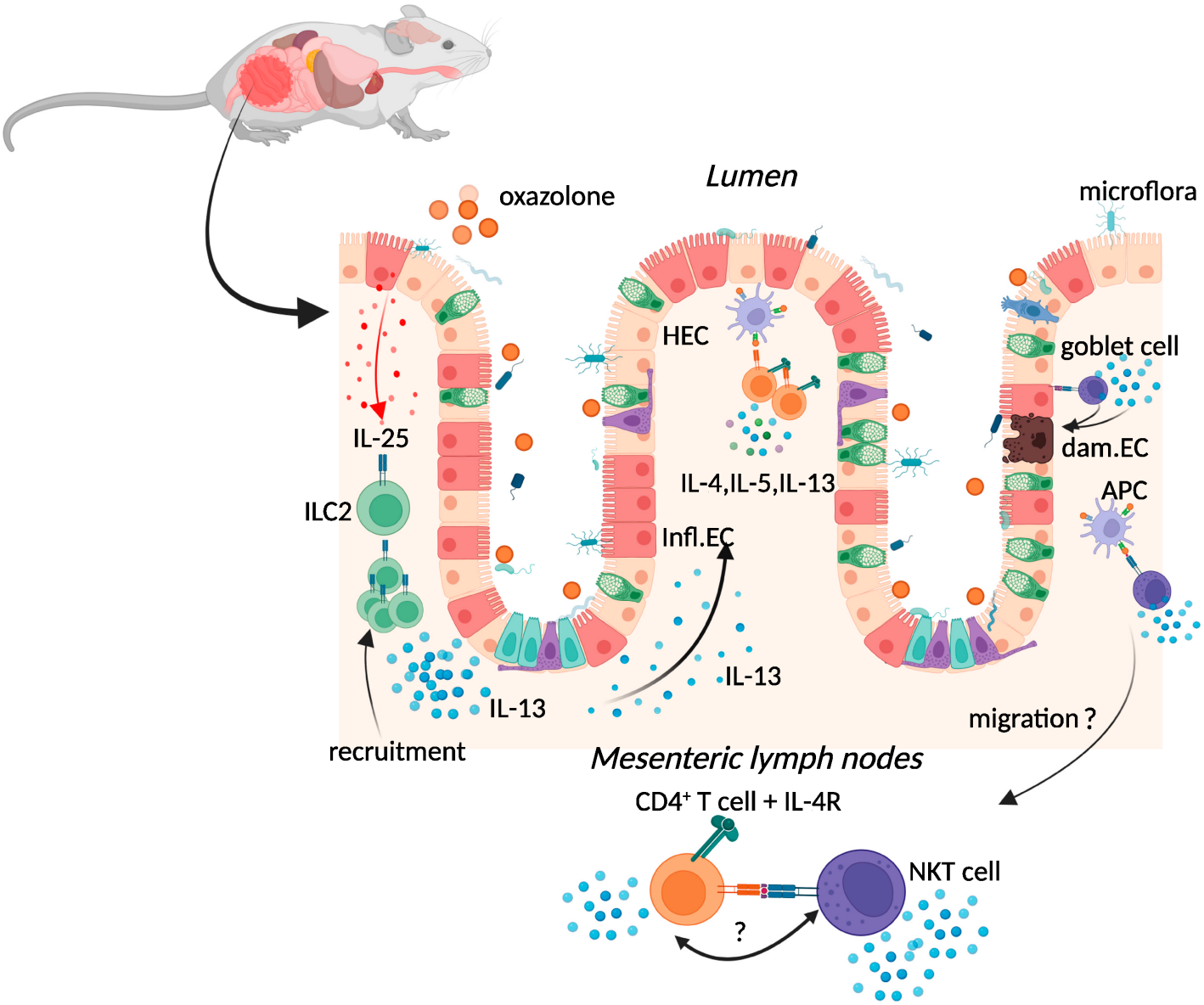

Figure 1. Immune response during oxazolone colitis. Oxazolone administration results in the production of IL-25, activation of ILC2, and production of IL-13, activating CD4+ T cell responses and amplifying type-2 cytokine production. Oxazolone administration also results in the expansion of T cells with surrogate markers of NKT cell function and IL-13 production by populations of CD1-restricted NKT cells. The resulting chronic inflammatory responses result in goblet cell depletion, increased intestinal permeability, and increased adhesion of commensal intestinal microbiota to the epithelium. Key: inflamed epithelial cells (Infl.EC), healthy epithelial cells (HEC), damaged epithelial cell (dam.EC). Created with BioRender.com, accessed on 18 August 2022.

Two methods of OC induction are currently employed to elicit either a self-resolving acute or a chronic response. The former is achieved by the single administration of an oxazolone enema, while the latter is preceded by a dermal pre-sensitisation five days before administration of an oxazolone enema, leading to chronic OC [7][8]. Both acute and chronic OC in mice are characterised by a superficial inflammation of the distal colon mucosa, a high volume of inflammatory infiltrate (neutrophils, macrophages, and lymphocytes), goblet-cell depletion, oedema

formation, epithelial cell loss, haemorrhage, and vascular dilation [7][9][10]. These histologic features, as well as the distribution of OC, resemble human UC [1].

Chronic activation of type-2 immune responses has been proposed to be the main driver of human UC [11] (**Figure 1**). In the murine model, oxazolone activation of the type-2 immune response is characterised by the production of interleukin (IL)-4 in the acute phase, then superseded by the production of IL-13 in the chronic phase [7][12][13][14]. Increased production of IL-13 (and IL-5) was also evident in lamina propria T cells isolated from UC patients [15]. Interestingly, the use of mice deficient in IL-4 receptor-alpha (IL-4Rα), a common receptor for both IL-4 and IL-13, resulted in the exacerbation of OC, which could only be rescued by depletion of IL-13 in these mice [16]. Moreover, OC was prevented in mice given an IL-13 receptor subunit alpha-2 (IL-13Rα2) fusion protein that neutralises IL-13 bioactivity [7], alluding to the possible involvement of IL-13 signalling in the exacerbation of IBD in both pre-clinical models and patients [17].

Although the initial cell source of IL-13 in UC is yet undetermined, both natural killer T cells (NKT) and conventional $CD4^+$ T cells secrete copious amounts of IL-13 during OC [7][16]. CD1d-restricted NKT cells expressing an invariant T-cell receptor can secrete IFN-γ or IL-4, activating $CD4^+$ T cells to become Th1 or Th2 cells (**Figure 1**) [18].

2.2. TNBS-Induced Colitis

This pre-clinical model also utilises intrarectal administration of a haptenising agent in ethanol: 2,4,6-trinitrobenzene sulfonic acid (TNBS). Administration of 0.5 mg of TNBS in 50% ethanol to mice resulted in chronic transmural colitis, characterised by diarrhoea, weight loss, and rectal prolapse, pathology that mimics some characteristics of CD in humans [4]. Although one administration of TNBS resulted in acute chemical damage to the gut epithelium, inflammation was self-limiting, rather than the chronic inflammation seen in human disease [4]. Differing responses in mice are apparent in this acute model of colitis, varying according to several factors including age, genetic background, and TNBS dose [19]. To achieve chronic colitis, this model was developed by pre-sensitising the skin with 1% TNBS, followed by up to six repeated weekly intrarectal administrations of increasing doses of TNBS [14]. This model resembled the chronic phase of CD and was accompanied by production of IL-23 and IL-17 by lamina propria cells [20].

Isolated lamina propria $CD4^+$ T cells from mice given TNBS secreted high levels of the Th1 cytokine interferon (IFN)-γ, resembling the cytokine profile produced by isolated lamina propria $CD4^+$ T cells from CD patients [21]. This distinguished them from the Th2 profile of the same cells isolated from UC patients, or mice given oxazolone [21]. Although antibodies against IL-12, a pivotal cytokine for Th1 differentiation, abrogated established colitis and the initiation of TNBS-disease in BALB/c mice [4], TNBS-dependent colitis was exacerbated in IFN-γ-deficient mice on a BALB/c background [22].

The clinical importance of the TNBS model is demonstrated by the translation of Neurath's anti-IL-12 antibody findings from TNBS murine experiments to successful human trials [23]. Importantly, the antibody used in these same studies was later found to react with the promiscuous p40 subunit shared by both IL-12 (a 70 kDa

heterodimer of the p40 and a p35 subunit) and IL-23 (heterodimer of the p40 and a p19 subunit) (summarized in [24]). Clinical trials with “brakinumab”, a monoclonal antibody recognising the human p40 subunit, downregulated both IL-12p70 and IL-23 secretion [25] and resulted in a clinical improvement in patients with active CD [26]. Drug development of brakinumab was discontinued due to the existence of another IL-12/IL-23 inhibitor, Stelera (ustekinumab), on the market, which significantly increased the induction and maintenance of clinical remission in patients with UC [27]. Despite the findings of exacerbated TNBS-colitis in mice lacking the p19 subunit of IL-23, novel therapies targeting IL-23 and the IL-23R have been developed and deemed successful when tested in clinical trials of patients with IBD [28].

2.3. Dextran-Sulphate-Sodium-Induced Colitis

Dextran sulphate sodium (DSS) colitis is the most widely used experimental murine model of colitis, established by Okayasu in 1990 through the administration of DSS with a molecular weight of 40–50 kDa in drinking water [5]. DSS is thought to form nano-lipid vesicles with medium-chain fatty acids (MCFAs) in the colon, which fuse with colonocyte membranes and increase inflammatory cytokine levels [29]. A high-fat diet rich in MCFAs exacerbated weight loss, inflammatory cytokine expression, and colon shortening in this model, with dodecanoic acid favouring disruption of intestinal barrier function and increased vesicle formation in vitro [29]. One day after administration, DSS particles were present systemically in Kupffer cells of the liver, in macrophages of the mesenteric lymph node, and in the lamina propria of the large intestine [30]. DSS administration was also characterised by erosion of the intestinal epithelium, inflammatory infiltration of the large intestine, and dysbiosis of the intestinal microbiome [5]. While these features are similar to those found in human disease, the transmural inflammation apparent in TNBS-colitis is absent in this model [31]. Although repeated rounds of DSS can be administered to provide the pattern of remitting, relapsing inflammation in human IBD, some of the limitations of this model include inter-batch variability of DSS and the need to optimise DSS dose, given the impact of the intestinal microbiome on disease [31][32].

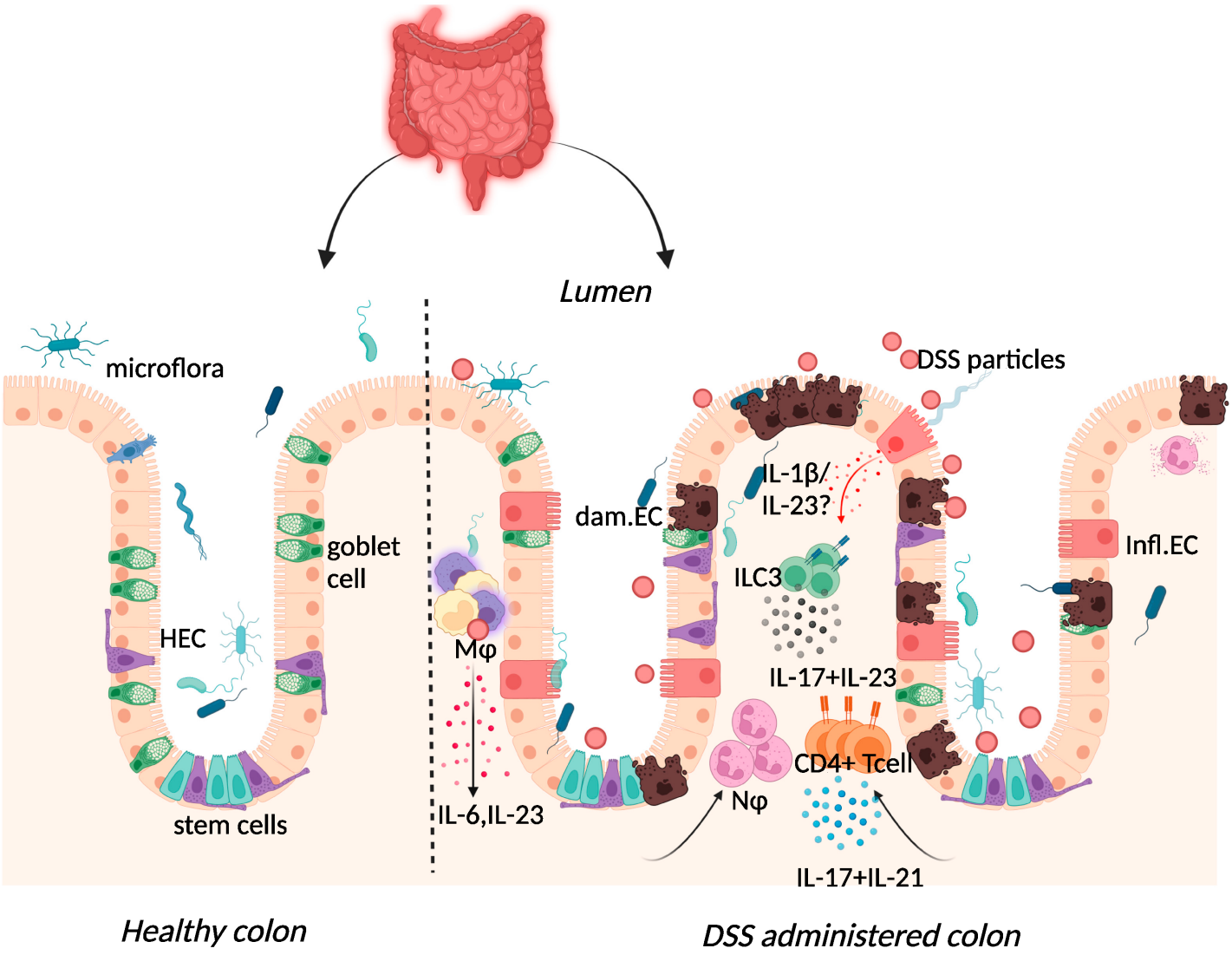

Figure 2. Immune response to DSS administration. DSS administration results in epithelial release of IL-1β, activation of ILC3, and release of IL-23. IL-23 release results in the influx of neutrophils and CD4+ T cells, which further respond through enhanced IL-17 signalling. The resulting chronic inflammatory responses result in goblet cell depletion, increased intestinal permeability, and increased adhesion of commensal intestinal microbiota to the epithelium. Key: Inflamed epithelial cells (Infl.EC), healthy epithelial cells (HEC), damaged epithelial cell (dam.EC), macrophages (MΦ), neutrophils (NΦ). Created with BioRender.com, accessed on 18 August 2022.

DSS-colitis can be induced in immunodeficient mice including recombination-activating gene (RAG)-1-deficient and severe combined immune deficient (SCID) mice, suggesting the dispensability of the adaptive immune system in initiating disease [33][34]. Although Kim et al. demonstrated colitis induction in RAG-1-deficient mice, the resultant mild colitis in these mice compared to their wild-type counterparts insinuates that lymphocytes may be necessary for subsequent colitis progression [34]. Histological assessment of biopsy specimens from IBD patients correlated UC and CD with severe mononuclear cell infiltration and basal plasmacytosis (plasma B cells) [35]. In the acute phase of the DSS-colitis model, this infiltrate consisted of innate macrophage, neutrophil, and eosinophil populations recruited following increased cytokine and chemokine expression [36].

Elevated expression of IL-17 and IL-23 was reported in IBD patients and in DSS-colitis, where expression of the two cytokines was intertwined (**Figure 2**) [25][37][38][39][40][41]. The use of the DSS-colitis model to test the role of these cytokines in disease has revolutionised not only the possible interventions available for patients but has also developed our understanding of mucosal immunology. At steady state, the p19 subunit of IL-23 is highly expressed within Peyer's patches and the thymus, as well as in polarised Th1 cells, activated macrophages, and dendritic cell populations derived from peripheral blood [42]. IL-23 induced proliferation of memory T cells and elevated secretion of IL-17 in vitro [43]. Subsequently, IL-23 signalling within intestinal epithelial cells was found to play an important role in protection against DSS colitis by regulating regenerating-islet-derived protein 3-beta (Reg3β)-dependent control of flagellated intestinal bacterial abundance and promoting IL-22 production [44]. Indeed DSS-colitis was exacerbated in IL-22-deficient mice [45] and blockade of IL-22 expression delayed recovery from DSS-colitis and exacerbated disease scores [46].

3. Spontaneous Colitis

3.1. Ikk-γ (NEMO) Deficiency Colitis

Conditional ablation of the NF-kB essential modulator (NEMO), also known as I-kappa-B kinase gamma (Ikk-γ), within the intestinal epithelium, resulted in spontaneous colitis in mice [3]. Chronic disease in intestinal-epithelial-cell-specific NEMO-deficient mice was associated with TNFR1-dependent colonic epithelial cell death, compromised epithelial integrity, bacterial translocation in the colon, immune cell infiltration, and increased expression of pro-inflammatory cytokines including TNF-α [3]. Absence of disease in double-deficient ($NEMO^{IEC-KO}$ + $MYD88^{-/-}$) mice, lacking NEMO and the important bacterial sensor myeloid differentiation primary response 88 (MYD88), supported a role for the gut microbiota in driving colitis [3]. Indeed $NEMO^{IEC-KO}$ mice raised under germ-free conditions did not develop spontaneous colitis, whereas co-housing of these mice with specific pathogen-free animals restored disease [47].

3.2. Interleukin-10 (IL-10) Deficiency Colitis

Although IBD is common among adults, childhood IBD constitutes about a quarter of all patients with IBD [48]. Approximately 15% of childhood IBD occurs in children <6 years old and is termed very early onset IBD (VEO-IBD) [49]. While most childhood IBD cases are polygenic in nature, many children with VEO-IBD have an underlying monogenetic disorder that results in severe enterocolitis, including mutations in IL-10 and/or IL-10R (summarized in [50]). Mice deficient in IL-10 develop spontaneous enterocolitis, characterised by progressive cellular infiltration of the cecum, colon, rectum, and small intestine, with transmural lesions and a high incidence of colorectal adenocarcinomas observed in 6-month-old mice [2][51]. Mice lacking IL-10 receptor β also developed spontaneous enterocolitis [52][53]. However, this receptor is shared with other type II cytokine receptors including those specific for IL-22, IL-26, and lambda interferons, in addition to IL-10 [54].

An important role for the gut microbiota in influencing the general enterocolitis seen in IL-10-deficient mice was implicated by a lack of disease in mice housed in specific pathogen-free conditions, or in germ-free conditions [2]

[55]. Treatment of IL-10-deficient mice with two different antibiotics, both shown to improve scores in patients with Crohn's disease [56][57], attenuated the development of spontaneous colitis [58]. Similar to IBD patients, colitic IL-10-deficient mice exhibited a markedly reduced species diversity in their faecal microbiome when compared to disease-free controls [55][59][60]. In addition, IL-10/IL-22 double-deficient mice lacking colitis exhibited higher microbial diversity when compared to IL-10-deficient mice [59].

4. Immune Cell Induced Colitis

T-Cell Adoptive Transfer Model

The transfer of murine CD45RB^{high}CD4^{+} T cells from healthy donors to severe combined immunodeficiency (SCID) (**Figure 3**) mice resulted in the development of a lethal wasting disease, an influx of inflammatory cells, and increased inflammatory cytokine production in the colon of the recipient [6].

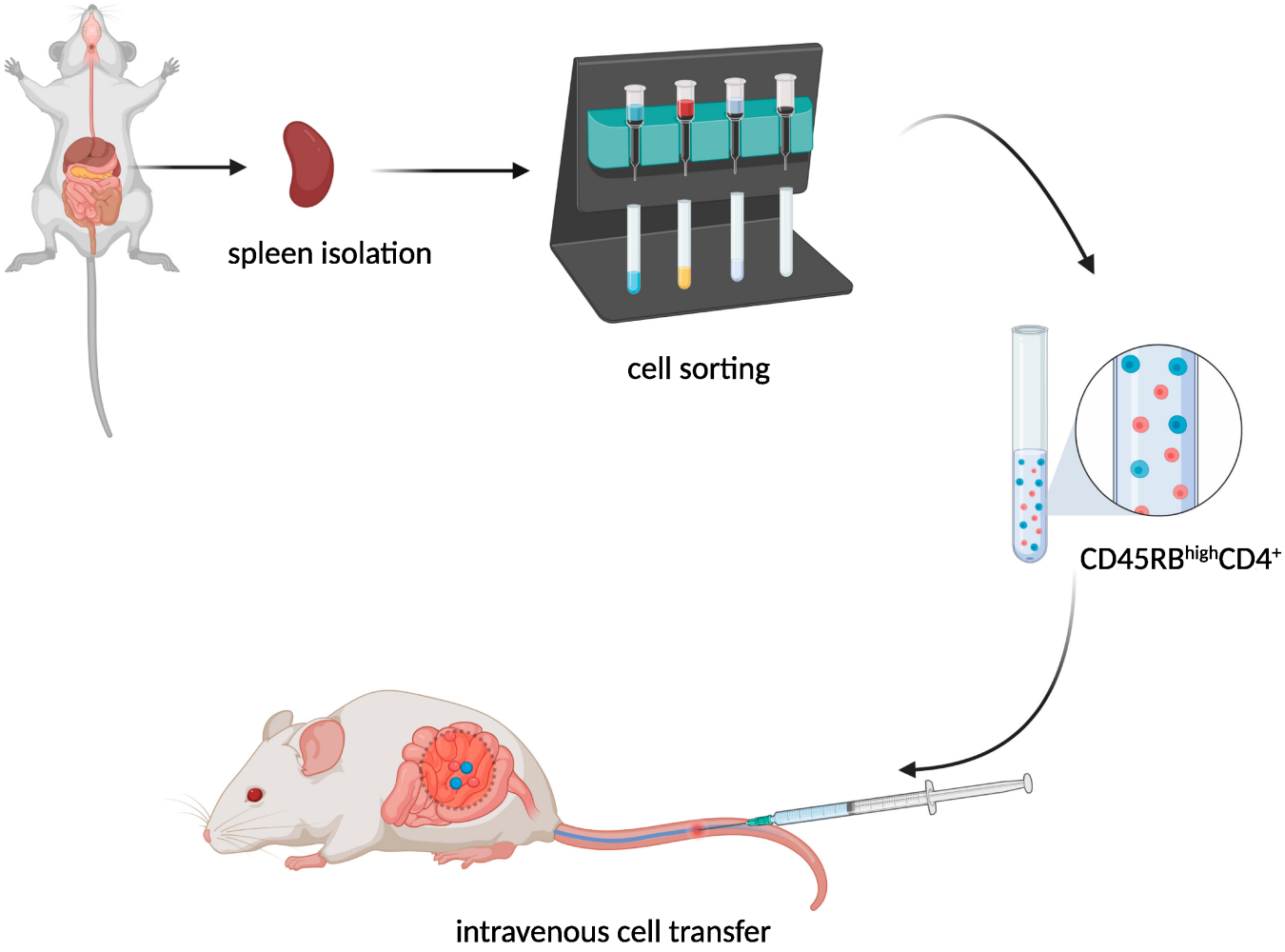

Figure 3. CD45RB^{hi}CD4^{+} T cell adoptive transfer scheme. Created with BioRender.com, accessed on 18 August 2022.

The resulting chronic colitis that developed within 5–8 weeks was T cell dose-dependent, and despite the presence of transferred T cells in several organs, significant pathology was limited to the large intestine [6]. Interestingly, the transfer of naïve CD45RB^{high}CD4^{+} cells into SCID mice with a reduced microbiota significantly reduced colitis when compared to SCID mice housed in SPF conditions [61]. Restoration of T-cell proliferation in germ-free *RAG*-deficient mice following reconstitution with cecal bacterial lysate-pulsed dendritic cells and induction of colitis in SPF *RAG*-deficient mice following the transfer of T cells specific for a microbiota flagellin antigen cemented the role of the commensal microbiota in driving disease in this model [62].

Although both CD45RB^{low} and CD45RB^{high}CD4^{+} T cells homed to the intraepithelial and lamina propria compartments of both the small and large intestine [61], CD45RB^{low} or total unfractionated CD4^{+} T-cells were incapable of inducing colitis [6]. Following the discovery that the CD45RB^{low} population comprised a population of CD4^{+}CD25^{+} regulatory T cells that could cure colitis in SCID or *RAG1*-deficient recipients of CD4^{+}CD45RB^{high} T cells [63], the T-cell transfer model of colitis was further refined by reconstitution of SCID mice with CD25-depleted CD4^{+} cells [64]. Although colitis in this model was accredited to the production of the Th1 cytokine IFN-γ [6][65], enhanced emergence of IL-17A^{+}IFN-γ population of T cells and suppression of populations of Foxp3^{+} and IL-10-producing regulatory T cells was attributed to IL-23R signalling in T cells [66]. Similarly, an absence of IL-23 in IL-12p19-deficient *RAG*-deficient recipients resulted in significantly decreased levels of proinflammatory cytokine production in the intestine [67]. While intestinal inflammation was significantly reduced in the *RAG*-deficient recipients of IL-23R-deficient CD45RB^{high}CD4^{+} T cells, or p19$^{-/-}$RAG$^{-/-}$ recipients of CD4^{+}CD25^{-}CD45RB^{high} T cells, these mice still exhibited systemic inflammation and weight loss [66][67], suggesting a tissue-restricted activity of IL-23.

Using IFN-γ-deficient RAG$^{-/-}$ recipients, IFN-γ was subsequently shown to be dispensable for the induction and progression of CD4^{+}CD25^{-}CD45RB^{high} T cell transfer colitis [68]. Inflammatory responses in these recipients favoured IL-17A production, where neutralisation of IL-17A/F significantly reduced weight loss and histopathological score in these animals [68]. A population of CD4^{+}IL-17F^{+} T cells was sufficient to induce colitis in *RAG1*-deficient recipients, where the transition of these precursors to Th1-like cells was an absolute requirement for disease [69]. Interestingly, IL-21 signalling was recently proposed to dampen T-cell transfer colitis by reducing IL-17A production and augmenting IL-22 production in populations of ILC3s [70].

An advantage to this model is the ability to examine early immunological events associated with gut inflammation, including regulatory T cells responses. In addition, the apparent inflammatory response in both the small bowel as well as the colon makes this model ideal for the study of CD [65]. However, the SCID and *RAG*$^{-/-}$ recipients used in this model spontaneously develop T and B cell populations as they age [71], while NK cells from *RAG*$^{-/-}$ mice are reported to exhibit altered function and fitness [72]. The lower prevalence of human SCID patients, estimated at 1 in 58,000 new-borns in the United States (0.0017%) [73], compared to a higher incidence of CD (estimated at 10.7 cases per 100,000 individuals in the United States (0.0107%) [48], points to a factorial model of CD induction/development, independent of primary immunodeficiencies in T and B cells. This excludes this model as an exact model of CD, despite the many similarities.

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